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This is a request for filing a Provisional Application for Patent under 37 CFR 1.53(c)

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Title: SYNTHESIS AND EVALUATION OF SUBSTITUTED 4-ARYLOXY AND 4-ARYLSULFANYL-PHENYL-2-AMINOTHIOAZOLES AS INHIBITORS OF HUMAN BREAST CANCER CELL PROLIFERATION

20 Sheets of specification.

_____ Sheets of drawings.

University of Virginia Patent Foundation claims small entity status as a nonprofit organization (37 CFR §§1.27(a)(3) and (c)). The Commissioner is hereby authorized to charge the Small Entity Fee of $80 to Deposit Account No. 50-0423.

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YES ☐ NO ☒ Grant No. _____

Dated: October 27, 2003

Respectfully submitted,

By: _____
John P. Breen (Reg. No. 38,833)

Synthesis and Evaluation of Substituted 4-Aryloxy-and 4-Arylsulfanyl-phenyl-2-aminothioazoles as Inhibitors of Human Breast Cancer Cell Proliferation

Background

Breast cancer is the most common cancer and second most cause of cancer death among women. The National Cancer Institute (NCI) estimates 211,000 new breast cancer cases and 40,000 deaths for 2003. There are two types of breast cancer: in situ and invasive. In situ breast cancer is divided into two subtypes: ductal cystic (DCIS) and lobular cystic (LCIS). Infiltrating ductal carcinoma is the most common type of invasive breast cancer accounting for approximately 70% of all breast cancer diagnoses. Another type of invasive breast cancer is infiltrating lobular carcinoma. This form accounts for 5-10% of invasive breast cancers. In addition, there are a few less common histologic subtypes of invasive cancer including medullary, mucinous, and tubular.

Current treatments for breast cancer depend on the patient's type of breast cancer. Local incision plus radiation or a simple mastectomy are possible treatment options for patients with DCIS. There is a 20-30% risk of developing invasive breast cancer for women with LCIS and as a result, it is managed with careful bilateral breast observation. Invasive cancers are treated surgically by either a modified radical mastectomy with axillary lymph node dissection or a lumpectomy with axillary lymph node dissection followed by local radiation. Surgical treatment options are standard treatment therapies for DCIS and invasive cancers followed by post-surgical (adjuvant) treatment. These adjuvant therapies have improved survival rates of women with these types of breast cancer. In addition to surgical options, adjuvant drug therapy can decrease the risk of systemic recurrence by approximately one third.

Adjuvant treatments include cytotoxic chemotherapy (i.e. paclitaxel, doxorubicin), hormonal therapy (i.e. tamoxifen), or a combination of the two: These treatments are not without severe side effects. Paclitaxel inhibits microtubule disassembly and is active against a wide range of human tumors. The major side effects of paclitaxel are neutropenia, neurotoxicity, and cardiotoxicity. Doxorubicin is one of the most active cytotoxic agents against breast cancer, but side effects, such as cardiotoxicity and myelosuppression, have hindered this drug's use in adjuvant therapy. Tamoxifen is the only drug approved by the United States Food and Drug Administration for breast cancer risk reduction in estrogen-sensitive breast cancer. Women receiving tamoxifen may experience more frequent hot flashes, the development of cataracts, and increased risk for venous thromboembolic events and strokes. Tamoxifen use is also associated with

increased endometrial cancer risk in postmenopausal women with a uterus. As a result of the side effects caused by the current adjuvant treatments, there is a need for safer, more potent breast cancer agents.

2-Aminothiazoles represent a fairly new class of breast cancer drugs with only a few examples in the literature (Figure 1). Currently, a number of aminothiazolecarbonitriles [6] and thiazolylaminopyridines [7,8] are being investigated for their use as tyrosine kinase inhibitors. Aminothiazole inhibitors of cyclin-dependent kinase 2 have been shown to have significant antitumor activity in breast cancer models.[9] Thiophene-2 carboxamidines containing 2-aminothiazoles have been evaluated as serine protease urokinase inhibitors.[10] In addition to 2-aminothiazoles, there are also few examples in the breast cancer literature of compounds containing diaryl ethers. A number of diaryl ether compounds have been evaluated as anti-cancer agents,[11] however, there are no reports of diaryl ethers with a 2-aminothiazole moiety. The present invention is directed to the synthesis of a number of 4-aryloxy- and 4-arylsulfanyl-phenyl-2aminothiazoles (Figure 2), pharmaceutical compositions comprising such compounds and their use as anticancer agents. The compounds are evaluated for efficacy against a panel of human breast cancer cell lines that represent a clinical spectrum of estrogen positive, estrogen-negative, and adriamycin-resistant breast cancers.

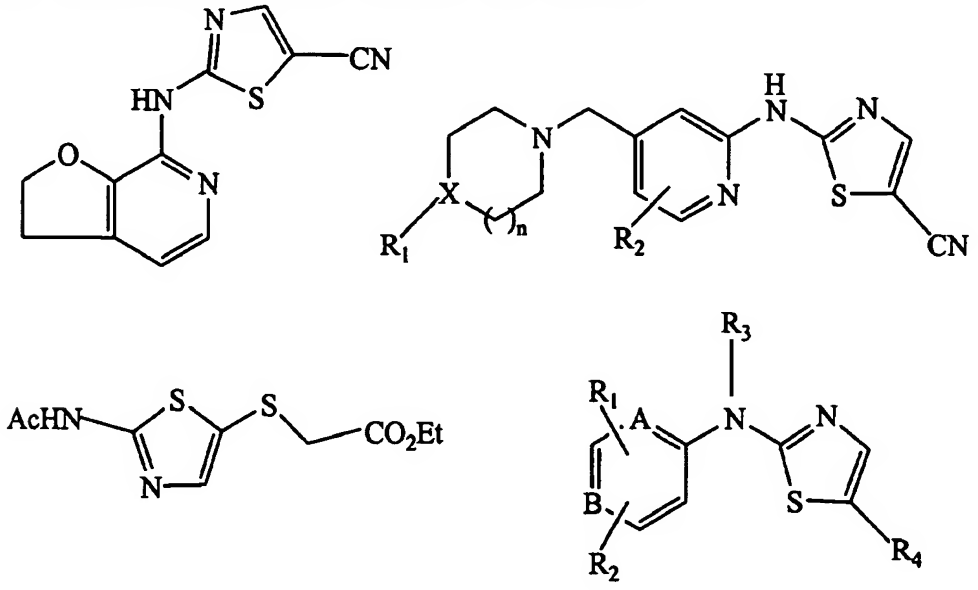


Fig. 1

Examples of current 2-aminothiazoles being investigated for breast cancer activity

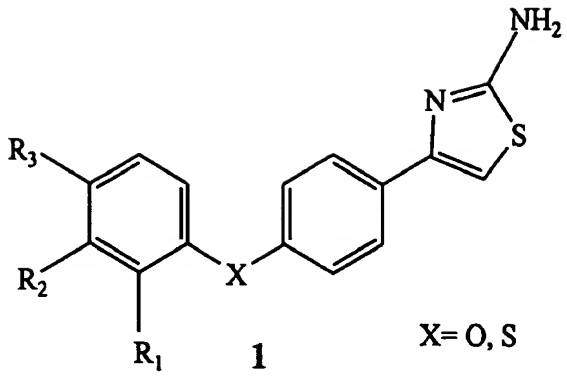


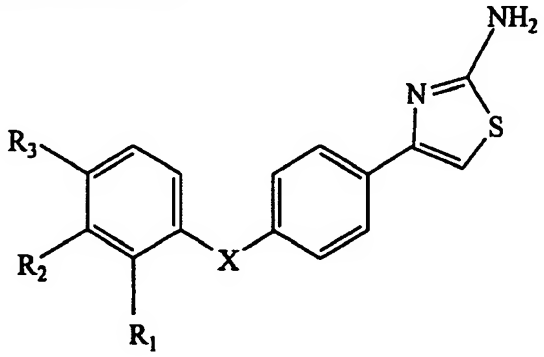
Fig. 2

General structure of 4-aryloxy- and 4-arylsulfanyl-phenyl-2-aminothiazole salts

Detailed Description

Several substituted 4-aryloxy- and 4-arylsulfanyl-phenyl-2-aminothiazoles have been synthesized and evaluated for cytotoxic activity against estrogen-positive, estrogen negative, and adriamycin-resistant human breast cancer cell lines. 4-[4' -'(3,4 Dichlorophenoxy)-phenyl]-thiazol-2-yl ammonium iodide demonstrated potent activity against both estrogen- positive and negative breast cancer cell lines with low micromolar (μlM) GI_{50} values. In addition, we have identified several 2-aminothiazoles that demonstrated selective potency for the adriamycin-resistant and estrogen-negative breast cancer cell lines. The results suggest that these 2-aminothiazoles represent lead compounds for evaluation in animal models of breast cancer.

In accordance with the present invention an anticancer agent is provided wherein the agent has the general structure:



I

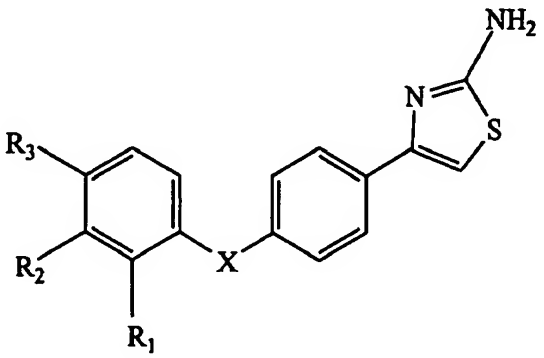
wherein X is selected from the group consisting of O, S and NH and R_1, R_2, and R_3 are independently selected from the group consisting of H, halo, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, aryl, -O-aryl and $(CO)OR_4$, wherein R_4 is H or $(C_1\text{-}C_4)$alkyl. In one embodiment, X is O or S

R_1 is H and R_2, and R_3 are independently selected from the group consisting of H, halo, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, phenyl, -O-phenyl and (CO)OR_4, wherein R_4 is (C_1-C_4)alkyl. In another embodiment the compounds has the general structure of Formula I, wherein X is O or S, R_1 is H and R_2, and R_3 are independently selected from the group consisting of H, Cl, (C_1-C_2)alkyl, (C_1-C_2)alkoxy, phenyl, -O-phenyl and (CO)OCH_2CH_3 and pharmaceutically acceptable salts thereof.

One embodiment of the present invention is directed to pharmaceutical compositions comprising the compounds of the invention and a pharmaceutically acceptable carrier. The pharmaceutically acceptable carrier can be selected from among the group consisting of excipients, disintegrating agents, binders and lubricating agents. The amount of the pharmaceutical agent suitable for administration will be in accordance with standard clinical practice. In addition the pharmaceutical compositions can be further combined with other known anti-tumor agents and used in conjunction with known anti-tumor therapies.

The anticancer compositions of the present invention can be administered either orally or parenterally. In one embodiment the composition is administered locally by injection or by an implantable time release device. When administered orally, the compounds can be administered as a liquid solution, powder, tablet, capsule or lozenge. The compounds can be used in combination with one or more conventional pharmaceutical additives or excipients used in the preparation of tablets, capsules, lozenges and other orally administrable forms. When administered parenterally, and more preferably by intravenous injection, the sodium channel blockers of the present invention can be admixed with saline solutions and/or conventional IV solutions.

In accordance with one embodiment of the present invention a method is provided for inhibiting the proliferation of neoplastic cells, and more particularly in one embodiment, breast cancer cells. The method comprises contacting the cells with a compound represented by the general structure:



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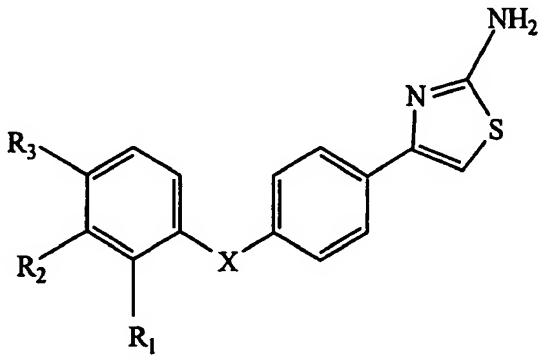
wherein X is selected from the group consisting of O, S and NH and R_1, R_2, and R_3 are independently selected from the group consisting of H, halo, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, aryl, -O-aryl and $(CO)OR_4$, wherein R_4 is H or $(C_1$-$C_4)$alkyl. In one embodiment, X is O or S R_1 is H and R_2, and R_3 are independently selected from the group consisting of H, halo, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, phenyl, -O-phenyl and $(CO)OR_4$, wherein R_4 is $(C_1$-$C_4)$alkyl. In another embodiment the compounds has the general structure of Formula I, wherein X is O or S, R_1 is H and R_2, and R_3 are independently selected from the group consisting of H, Cl, $(C_1$-$C_2)$alkyl, $(C_1$-$C_2)$alkoxy, phenyl, -O-phenyl and $(CO)OCH_2CH_3$ and pharmaceutically acceptable salts thereof.

In accordance with one embodiment of the present invention a method is provided for treating a warm blooded vertebrate patient, including humans, afflicted by a neoplastic disease, such as breast cancer. The method comprises the steps of administering to such a patient an effective amount of a composition comprising a compound represented by the general structure:



I

wherein X is selected from the group consisting of O, S and NH and R_1, R_2, and R_3 are independently selected from the group consisting of H, halo, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, aryl, -O-aryl and $(CO)OR_4$, wherein R_4 is H or $(C_1$-$C_4)$alkyl and pharmaceutically acceptable salts thereof. In one embodiment, X is O or S, R_1 is H and R_2, and R_3 are independently selected from the group consisting of H, halo, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, phenyl, -O-phenyl and $(CO)OR_4$, wherein R_4 is $(C_1$-$C_4)$alkyl. In another embodiment the compounds has the general structure of Formula I, wherein X is O or S, R_1 is H and R_2, and R_3 are independently selected from the group consisting of H, Cl, $(C_1$-$C_2)$alkyl, $(C_1$-$C_2)$alkoxy, phenyl, -O-phenyl and $(CO)OCH_2CH_3$ and pharmaceutically acceptable salts thereof. In one embodiment X is O, R_1 is H, R_2 is selected from the group consisting of H, Cl, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, phenyl, -O-phenyl, and $(CO)OR_4$, and R_3 is selected from the group consisting of H, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, phenyl, -O-phenyl and $(CO)OR_4$, wherein R_4 is $(C_1$-$C_4)$alkyl.

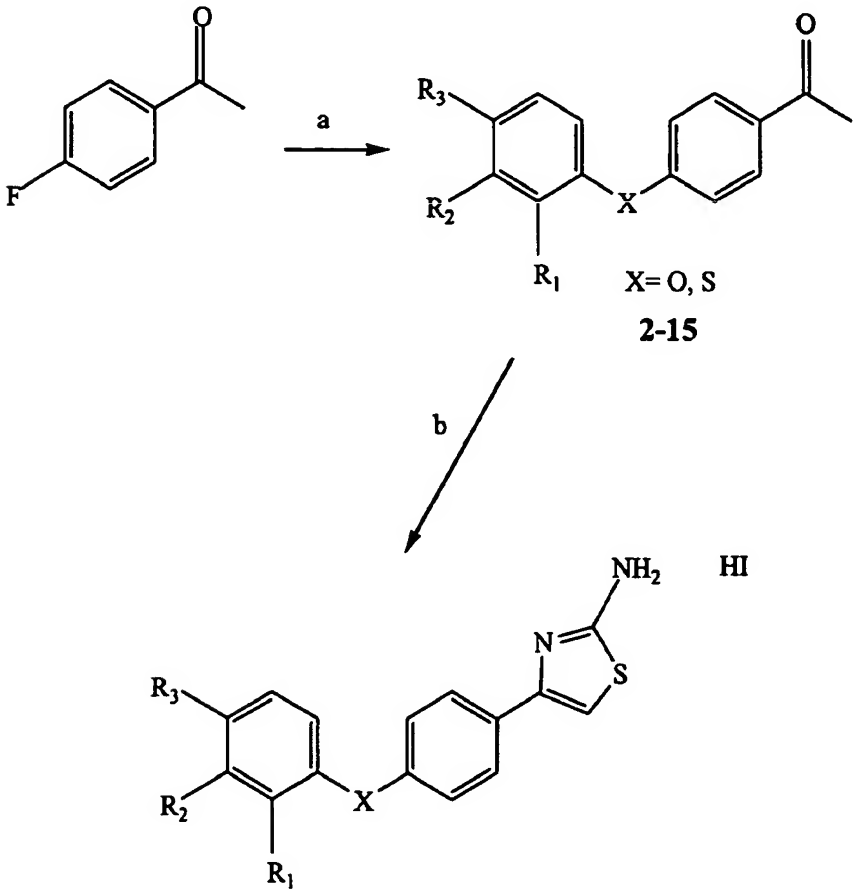
Example 1

In vitro activity of the 4-aryloxy- and 4-arylsulfanyl-phenyl-2 aminothiazole compounds

Results and Discussion

A general synthesis of the substituted 4-aryloxy- and 4-arylsulfanyl-phenyl-2 aminothiazole salts is shown in Scheme 1.

Scheme 1



Reagents and conditions: a) phenol or thiol, K_2Co_3, DMAC, reflux, $_{8\text{-}10}$ h, $_{38\text{-}93}$%; b) thiourea, I_2, Etoh, 100°C, 3 h, 40-98%

Condensation of the appropriately substituted phenols with 4 '-fluoroacetophenone afforded the corresponding 4-aryloxyacetophenones in 40-93% yield.**12** This condensation reaction also

proceeded smoothly with various substituted benzenethiols forming the 4-arylsulfanylacetophenones in 38-87% yield. Treatment of the acetophenones with thiourea and iodine successfully generated the 2 aminothiazole salts (Table 1) in 40-98% yield. 13

Upon completion of the synthesis, thiazole compounds **17-24** and **27-30** were submitted to the NCI's antitumor screen and the results against human breast cancer cell lines are shown in Table 2 as GI_{50} values. Analogues **16, 25,** and **26** were evaluated for growth inhibition of MCF- 7 at 100 μM. Compounds **20** and **28** showed selectivity for the adriamycin-resistant cell line with GI_{50} values of 1.29 μM and 3.37 μM, respectively. Adriamycin-resistant selectivity is clinically important because patients develop cancer that is resistant to treatment.

Interestingly, when the GI_{50} values of compounds **17** (X=O) and **27** (X=S) are compared, there appears to be a relationship between heteroatom substitution and selectivity for the estrogen-positive or estrogen-negative cell lines. The GI_{50} of **17** exceeded 100 μM in all cell lines except for the estrogen-positive cell line T-47D in which the GI_{50} was 0.917 μM, while the GI_{50} of **27** was 24.4 μM for the T -47D cell line.

Compound **27** showed greater selectivity for the estrogen-negative cell line MDA-MB 435 with a GI_{50} of 1.49 μM when compared with greater than 100 μM for **17**. The aforementioned selectivity was also seen for **22** and **30** for the same cell lines. These results strongly suggest that estrogen-positive selectivity appears to be achieved using an oxygen linkage whereas compounds with a sulfur linkage are significantly more active against estrogen-negative breast cancer cell types. Thiazole **20** exhibited low micromolar cytotoxicity in all breast cancer cell lines except T-47D and was the only compound to show significant cytotoxicity in the estrogen-negative HS-578T cell line with a GI_{50} of 2 μM. Low micromolar cytotoxicity was also observed for **28** which was active in all cell lines except HS 578T with GI_{50} values in the 1-5 μM range. Compounds **20** and **28** have similar 3,4-dichloro substitutions on their outer phenyl ring and differ only in the heteroatom that links the two rings. Thiazoles **22-24** demonstrated selectivity for the estrogen-positive cell line T-47D with GI_{50} values of 0.54 μM, 3.91 μM, and 4.90 μM, respectively. Compound **30** was selective against the MDA-MB-435 cell line with a GI_{50} of 1.4 μM. In addition to the selectivity attained with different linkages between the two phenyl rings, these thiazoles also exhibit several distinct structure-activity relationships for substitution on the outer phenyl ring.

For the oxygen linker series, thiazole **22** with an electron-donating para-methyl substituent shows increased efficacy over the electron-withdrawing para-chloro thiazole **17** in all cell lines. An increase in bulk at the para position from methyl to phenyl does

not significantly alter activity. Chlorine substitution at the ortho, meta, and para positions was also investigated with compounds **17-19**. In most of the cell lines, the best activity was achieved by chloro substitution at the meta position. Substitution at the ortho position showed a slight decrease in activity whereas the para-chloro thiazole had GI_{50} values greater than 100 μM in all cell lines except T -47D. Although the meta- and para chloro thiazoles were less active than the ortho-chloro compound, chlorine substitution at both the meta and para positions provided the most active compound out of this series. While a para electron-donating group was more active (compared GI_{50} of **22** to that of **17**) than a para electron-withdrawing group for the oxygen linker series, the opposite relationship was observed for compounds with the thioether linkage. Generally, for this series of compounds, the para chloro thiazole was more active (compared GI_{50} of **27** to that of **30**) than the para-methyl thiazole.

Conclusion

In conclusion, we have synthesized a series of 4-aryloxy- and 4-arylsulfanyl-phenyl-2 aminothiazoles. Compounds **17, 18, 22, 24, 27, and 30** demonstrated selective cytotoxicity of either estrogen- positive or negative breast cancer cells while compounds **20** and **28** showed low micromolar growth inhibition of most human breast tumor cells. In general, thiazoles with an oxygen linkage showed estrogen-positive selectivity whereas estrogen-negative selectivity was achieved by thioether linkages. Thiazoles **20** and **28**, both with 3,4-dichloro substitutions, exhibited selectivity for the adriamycin resistant cell line. These compounds have the potential to be promising lead compounds for mechanistic studies on breast cancer cell cycle arrest and for the further development of selective thiazole-containing breast cancer agents.

Experimental Section

All starting materials were purchased from Aldrich and were used as received. Melting points were measured on an Electrothermal Mel- Temp and are uncorrected. Carbon and proton NMR spectra were recorded on a General Electric 300 MHz spectrometer. Mass spectra were obtained on a Finnagan LcQ Classic spectrometer. High resolution (EI) mass spectra were obtained from the University of Illinois, Urbana-Champaign. Combustion analyses were performed by Atlantic Microlabs Inc.

General Procedure for Synthesis of 4-Aryloxy and 4-Arylsulfanyl Substituted Acetophenones[12] **(2-15)**. Anhydrous K_2CO_3 (12 mmol) was added to a solution of 4'-

fluoroacetophenone (10 mmol) and the corresponding phenol or thiol (10 mmol) in N,N-dimethylacetamide (DMAC, 10 mL). The suspension was refluxed for 8-10 h, cooled to room temperature, and diluted with H_2O (10 mL). In some instances (**8** and **9**), the addition of H_2O resulted in the deposition of the product as a solid which was collected by filtration. In those instances where the product was not a solid, the resulting solution was extracted with $CHCl_3$ (3 × 15 mL), dried over $MgSO_4$, and concentrated *in vacuo* to yield a brown oil. The remaining DMAC was removed by Kugelrohr distillation. The viscous oil was allowed to cool and solidify. The crude solid was recrystallized from EtOH.

4-(4'-Chlorophenoxy)-acetophenone (2). Isolated as a light brown solid (1.81 g, 73%); mp 65-66 °C (lit.[12] 66-68 °C); ^{1}H NMR ($CDCl_3$) δ 2.57 (s, 3H), 6.99 (d, J = 6.4 Hz, 4H), 7.35 (d, J = 8.3 Hz, 2 H), 7.94 (d, J = 8.2 Hz, 2H); ^{13}C NMR δ 27.0, 117.8, 121.7, 130.2, 130.6, 131.2, 132.8, 154.7, 162.0, 197.1; MS APCI *m/z* 247 $(M)^+$.

4-(3'-Chlorophenoxy)-acetophenone (3). Isolated as an orange oil (2.03 g, 82%); ^{1}H NMR ($CDCl_3$) δ 2.49 (s, 3H), 6.82-7.13 (m, 5H), 7.22 (t, J = 7.9 Hz, 1H), 7.88 (d, J = 7.7 Hz, 2H); ^{13}C NMR δ 26.9, 109.9, 118.3, 118.5, 120.6, 125.0, 131.1, 133.0, 135.7, 157.0, 161.4, 196.9; MS APCI *m/z* 247 $(M)^+$.

4-(2'-Chlorophenoxy)-acetophenone (4). Isolated as a yellow solid (1.64 g, 67%); mp 41-43 °C (lit.[16] 49-50 °C); ^{1}H NMR ($CDCl_3$) δ 2.47 (s, 3H), 6.85 (d, J = 8.3 Hz, 2H), 6.99-7.16 (m, 2H), 7.21 (d, J = 7.5 Hz, 1H), 7.39 (d, J = 7.5 Hz, 1H), 7.86 (d, J = 8.3 Hz, 2H); ^{13}C NMR δ 26.9, 109.9, 116.8, 123.0, 126.7, 127.2, 128.9, 131.1, 131.5, 132.5, 151.2, 161.7, 196.9; MS APCI *m/z* 247 $(M)^+$.

4-(3',4'-Dichlorophenoxy)-acetophenone (5). Recrystallized from hexanes to afford a brown solid (2.61, 93%); mp 47-49 °C (lit.[17] 50-52 °C); ^{1}H NMR ($CDCl_3$) δ 2.57 (s, 3H), 6.90 (d, J = 8.4 Hz, 1H), 7.01 (d, J = 8.5 Hz, 2H), 7.14 (s, 1H), 7.42 (d, J = 8.6 Hz, 1H), 7.95 (d, J = 8.3 Hz, 2H); ^{13}C NMR δ 27.0, 118.4, 119.7, 122.2, 128.5, 131.2, 131.8, 133.3, 134.0, 155.3, 161.2, 197.1; MS APCI *m/z* 281 $(M)^+$.

4-(4'-Methoxyphenoxy)-acetophenone (6). Isolated as a light brown solid (2.02 g, 84%); mp 56-58 °C (lit.[18] 61°C); ^{1}H NMR ($CDCl_3$) δ 2.55 (s, 3H), 3.81 (s, 3H), 6.90-7.00 (m, 6H), 7.90 (d, J = 7.9 Hz, 2H); ^{13}C NMR δ 26.9, 56.1, 115.6, 116.9, 122.2, 131.1, 131.9, 149.0, 157.2, 163.4, 197.2; MS APCI *m/z* 243 $(M)^+$.

4-(*p*-Toluoxy)-acetophenone (7). Isolated as a light brown solid (0.91 g, 40%); mp 44-46 °C; ^{1}H NMR ($CDCl_3$) δ 2.37 (s, 3H), 2.57 (s, 3H), 6.97 (d, J = 7.5 Hz, 4H), 7.19 (d, J = 7.7 Hz, 2H), 7.92 (d, J = 8.5 Hz, 2H); ^{13}C NMR δ 21.3, 26.9, 117.4, 120.5, 120.7, 131.1, 132.1, 134.9, 153.5, 163.0, 197.2; MS APCI *m/z* 227 $(M)^+$.

4-(Biphenyl-4'-yloxy)-acetophenone (8). Isolated as a pale yellow solid (2.61 g, 90%); mp 114-117 °C; ^{1}H NMR ($CDCl_3$) δ 2.59 (s, 3H), 7.06 (d, J = 8.3 Hz, 2H), 7.14 (d, J = 8.1 Hz, 2H), 7.36 (d, J = 8.0 Hz, 1H), 7.44 (t, J = 7.4 Hz, 2H), 7.60 (t, J = 7.1 Hz, 4H), 7.96 (d, J = 8.0 Hz, 2H); ^{13}C NMR δ 27.0, 117.9, 120.9, 127.5, 127.8, 129.2, 129.4, 131.1, 132.5, 138.2, 140.8, 155.5, 162.4, 197.2; MS APCI *m/z* 289 $(M)^+$.

4-(4'-Phenoxy-phenoxy)-acetophenone (9). Isolated as a white solid (2.47 g, 81%); mp 75-77 °C; ^{1}H NMR ($CDCl_3$) δ 2.57 (s, 3H), 6.80-7.40 (m, 11H), 7.94 (d, J = 8.1 Hz, 2H); ^{13}C NMR δ 26.9, 117.3, 119.2, 120.9, 122.1, 123.9, 130.3, 131.1, 132.3, 151.3, 154.5, 157.8, 162.9, 197.2; MS APCI *m/z* 305 $(M)^+$.

Ethyl 3-(4'-acetyl-phenoxy)-benzoate (10). Isolated as a yellow oil (1.92 g, 68%); ^{1}H NMR ($CDCl_3$) δ 1.37 (t, J =6.7 Hz, 3H), 2.56 (s, 3H), 4.35 (q, J = 7.1 Hz, 3H), 6.98 (d, J = 8.1 Hz, 2H), 7.24 (d, J = 7.9 Hz, 1H), 7.44 (t, J = 7.5 Hz, 1H), 7.71 (s, 1H), 7.86 (d, J = 7.5 Hz, 1H), 7.93 (d, J = 8.1 Hz, 3H); ^{13}C NMR δ 14.8, 26.9, 61.8, 118.0, 121.5, 125.0, 126.1, 130.5, 131.2, 132.8, 133.2, 156.1, 161.9, 166.2, 197.1; MS APCI *m/z* 285 $(M)^+$.

(4'-Phenylsulfanyl)-acetophenone (11). Isolated as an orange solid (0.87 g, 38%); mp 59-61 °C (lit.[19] 67-68 °C); ^{1}H NMR ($CDCl_3$) δ 2.55 (s, 3H), 7.21 (d, J = 8.1 Hz, 2H), 7.40-7.47 (m, 5H), 7.82 (d, J = 8.1 Hz, 2H); ^{13}C NMR δ 13.7, 128.0, 129.3, 129.4, 130.2, 132.6, 134.4, 135.0, 145.4, 192.9; MS APCI *m/z* 229 $(M)^+$.

4-(4'-Chloro-phenylsulfanyl)-acetophenone (12). Isolated as an orange solid (1.68 g, 64%); mp 40-42 °C; ^{1}H NMR ($CDCl_3$) δ 2.56 (s, 3H), 7.22 (d, J = 8.1 Hz, 2H), 7.38 (d, J = 6.5 Hz, 4H), 7.83 (d, J = 7.9 Hz, 2H); ^{13}C NMR δ 27.0, 128.3, 129.5, 130.4, 131.4, 135.4, 143.7, 144.5, 147.8, 197.5; MS APCI *m/z* 263 $(M)^+$.

4-(3',4'-Dichloro-phenylsulfanyl)-acetophenone (13). Isolated as a red oil (1.44 g, 87%); ^{1}H NMR ($CDCl_3$) δ 2.56 (s, 3H), 7.23-7.33 (m, 2H), 7.39-7.53 (m, 1H), 7.85 (d, J = 8.1 Hz, 4H); ^{13}C NMR δ 27.0, 129.4, 129.7, 131.6, 131.8, 132.3, 133.6, 133.9, 134.0, 134.5, 136.0, 197.5; MS APCI *m/z* 297 $(M)^+$.

4-(4'-Methoxy-phenylsulfanyl)-acetophenone (14). Isolated as a red solid (1.49 g, 58%); mp 25-27 °C; ^{1}H NMR ($CDCl_3$) δ 2.51 (s, 3H), 3.83 (s, 3H), 6.94 (d, J = 8.1 Hz, 2H), 7.07 (d, J = 8.1 Hz, 2H), 7.45 (d, J = 8.1 Hz, 2H), 7.76 (d, J = 8.1 Hz, 2H); ^{13}C NMR δ 26.9, 55.9, 115.9, 121.8, 126.3, 129.3, 134.4, 137.3, 147.4, 161.2, 197.6; MS APCI *m/z* 259 $(M)^+$.

4-(4'-Tolylsulfanyl)-acetophenone (15). Isolated as a red solid (1.64 g, 68%); mp 90-92 °C; ^{1}H NMR ($CDCl_3$) δ 2.40 (s, 3H), 2.54 (s, 3H), 7.15 (d, J = 8.1 Hz, 2H), 7.22 (d, J = 7.7 Hz, 2H), 7.41 (d, J = 7.5 Hz, 2H), 7.79 (d, J = 8.0 Hz, 2H); ^{13}C NMR δ 21.8, 27.0, 127.2, 128.4, 129.3, 131.0, 134.6, 135.0, 140.0, 146.4, 197.6; MS APCI *m/z* 243 $(M)^+$.

General Procedure for Synthesis of Substituted 4-Aryloxy and 4-Arylsulfanyl-phenyl-2-aminothiazole salts[13] (16-30).

Thiourea (40 mmol) and iodine (11 mmol) were added to a stirring solution of the appropriate acetophenone (10 mmol) in absolute ethanol (20 mL). The mixture was heated at 100 °C for 2-3 h in an open vessel. The crude residue was washed with ether (3 × 50 mL) and was recrystallized from hot water. A few of these compounds (**16**[20], **17**[21], and **26**[20]) in free amine or HCl salt form are reported in the literature.

4-(4'-Phenoxyphenyl)-thiazol-2-yl ammonium iodide (16). Isolated as a yellow solid (1.82 g, 46%); mp 193-195 °C; ^{1}H NMR (DMSO-d^6) δ 7.02 (t, J = 8 Hz, 4H), 7.08 (s, 1H), 7.13 (t, J = 6.2 Hz, 1H), 7.37 (t, J = 7.7 Hz, 2H), 7.65 (d, J = 8.1 Hz, 2H); ^{13}C NMR δ 103.0, 119.5, 120.1, 125.1, 128.8, 131.2, 140.1, 145.7, 156.4, 158.6, 171.1; MS APCI *m/z* 269 $(M\text{-}HI)^+$; Anal. calcd. for $C_{15}H_{13}IN_2OS$: C, 45.47; H, 3.31; N, 7.07. Found: C, 45.25; H, 3.26; N, 7.08.

4-[4'-(4-Chlorophenoxy)-phenyl]-thiazol-2-yl ammonium iodide (17). Isolated as a light orange solid (0.31 g, 71%); mp 152-154 °C; ^{1}H NMR (DMSO-d^6) δ 6.95-7.10 (m, 5H), 7.41 (t, J = 6.6 Hz, 2H), 7.67 (d, J = 8.7 Hz, 1H), 7.92 (d, J = 8.7 Hz, 1H), 8.94 (br s); ^{13}C NMR δ 109.8, 118.6, 118.8, 121.9, 123.1, 128.9, 131.0, 131.2, 131.7, 155.6, 170.0; HRMS calcd for $C_{15}H_{12}ClIN_2OS$ $(M\text{-}HI)^+$ *m/z* 303.036100, found *m/z* 303.035888.

4-[4-(3'-Chlorophenoxy)-phenyl]-thiazol-2-yl ammonium iodide (18). Isolated as a yellow solid (0.57 g, 65%); mp 107-110 °C; ^{1}H NMR (DMSO-d^6) δ 6.96 (d, *J* = 7.9 Hz, 1H), 7.11 (s, 1H), 7.18 (d, *J* = 8.1 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 1H), 7.70 (d, *J* = 8.2 Hz, 4H), 7.93 (d, *J* = 7.8 Hz, 1H), 8.96 (br s); ^{13}C NMR δ 103.2, 113.9, 118.4, 119.7, 120.2, 124.8, 128.9, 132.6, 135.0, 144.1, 157.6, 160.6, 171.0; HRMS calcd for $C_{15}H_{12}ClIN_2OS$ $(M\text{-}HI)^+$ *m/z* 303.036700, found *m/z* 303.035888; Anal. calcd. for $C_{15}H_{12}ClIN_2OS \cdot 0.6$ H_2O: C, 40.81; H, 2.72; N, 6.34. Found: C, 40.53; H, 2.60; N, 6.10.

4-[4-(2'-Chlorophenoxy)-phenyl]-thiazol-2-yl ammonium iodide (19). Isolated as a yellow solid (0.35 g, 40%); mp 160-163 °C; ^{1}H NMR (DMSO-d^6) δ 6.98 (d, *J* = 8.3 Hz, 2H), 7.08 (s, 1H), 7.17 (d, *J* = 8.1 Hz, 1H), 7.23 (t, *J* = 6.6 Hz, 1H), 7.37 (t, *J* = 7.7 Hz, 1H), 7.58 (d, *J* = 7.6 Hz, 1H), 7.68 (d, *J* = 8.3 Hz, 2H), 8.99 (br s); ^{13}C NMR δ 103.0, 118.2, 123.0, 126.9, 127.2, 128.9, 130.0, 131.7, 131.8, 133.4, 147.5, 158.3, 171.0; MS APCI *m/z* 303 $(M\text{-}HI)^+$; Anal. calcd. for $C_{15}H_{12}ClIN_2OS$: C, 41.83; H, 2.81; N, 6.50. Found: C, 41.65; H, 2.71; N, 6.48.

4-[4'-(3,4-Dichlorophenoxy)-phenyl]-thiazol-2-yl ammonium iodide (20). Isolated as a brown solid (0.35 g, 75%); mp 202-205 °C; ^{1}H NMR (DMSO-d^6) δ 7.07 (d, *J* = 7.5 Hz, 3H), 7.14 (s, 1H), 7.37 (s, 1H), 7.62 (d, *J* = 8.2 Hz, 1H), 7.70 (d, *J* = 8.1 Hz, 1H), 7.93 (d, *J* = 8.1 Hz, 1H), 9.02 (br s); ^{13}C NMR δ 103.4, 118.9, 120.2, 120.9, 121.7, 122.6, 129.0, 131.7, 132.7, 133.2, 133.5, 161.0, 171.1; HRMS calcd for $C_{15}H_{11}Cl_2IN_2OS$ $(M\text{-}HI)^+$ *m/z* 336.997000, found *m/z* 336.996915; Anal. calcd. for $C_{15}H_{11}Cl_2IN_2OS \cdot 0.9$ H_2O: C, 37.43; H, 2.28; N, 5.82. Found: C, 37.19; H, 2.25; N, 5.66.

4-[4'-(4-Methoxyphenoxy)-phenyl]-thiazol-2-yl ammonium iodide (21). Isolated as a yellow solid (0.37 g, 87%); mp 204-207 °C; ^{1}H NMR (DMSO-d^6) δ 3.71 (s, 3H), 6.95-

7.03 (m, 5H), 7.05 (s, 1H), 7.62 (d, J = 8.2 Hz, 2H), 7.98 (d, J= 7.9 Hz, 1H), 8.93 (br s); ^{13}C NMR δ 56.4, 102.6, 116.2, 117.1, 118.2, 122.1, 122.6, 124.5, 128.7, 131.6, 150.0, 171.1; MS APCI *m/z* 299 $(M\text{-}HI)^+$; Anal. calcd. for $C_{16}H_{15}IN_2O_2S$: C, 45.08; H, 3.55; N, 6.57. Found: C, 44.97; H, 3.65; N, 6.67.

4-[4'-(*p*-Toluoxy)phenyl]-thiazol-2-yl ammonium iodide (22). Isolated as a light brown solid (0.27 g, 65%); mp 118-120 °C; ^{1}H NMR (DMSO-d^6) δ 2.26 (s, 3H), 6.90-7.03 (m, 5H), 7.19 (t, J = 7.9 Hz, 2H), 7.65 (d, J = 8.6 Hz, 1H), 7.90 (d, J = 6.7 Hz, 1H); ^{13}C NMR δ 27.5, 117.6, 118.9, 120.3, 121.0, 128.6, 131.5, 131.6, 134.2, 134.9, 161.2, 162.6; MS APCI *m/z* 283 $(M\text{-}HI)^+$; Anal. calcd. for $C_{16}H_{15}IN_2OS$: C, 46.84; H, 3.69, N, 6.83. Found: C, 46.65; H, 3.86; N, 6.61.

4-[4'-(Biphenyl-4-yloxy)-phenyl]-thiazol-2-yl ammonium iodide (23). Isolated as a yellow solid (0.33 g, 70%); mp 253-254 °C; ^{1}H NMR (DMSO-d^6) δ 7.00-7.20 (m, 4H), 7.30 (d, J = 6.5 Hz, 1H), 7.40 (t, J = 7.3 Hz, 2H), 7.66 (m, 6H), 7.93 (d, J = 8.0 Hz, 1H); ^{13}C NMR δ 102.8, 119.8, 120.4, 127.4, 128.2, 128.8, 129.4, 129.5, 129.9, 136.7, 137.3, 156.4, 158.2, 159.4, 177.5; HRMS calcd for $C_{21}H_{17}IN_2OS$ $(M\text{-}HI)^+$ *m/z* 345.106200, found *m/z* 345.106160; Anal. calcd. for $C_{21}H_{17}IN_2OS$: C, 53.40; H, 3.63; N, 5.93. Found. C, 53.65; H, 3.65; N, 5.80.

4-[4'-(4-Phenoxy-phenoxy)-phenyl]-thiazol-2-yl ammonium iodide (24). Isolated as a pale yellow solid (0.42 g, 86%); mp 137-140 °C; ^{1}H NMR (DMSO-d^6) δ 6.95-7.12 (m, 10H), 7.34 (t, J = 7.4 Hz, 2H), 7.67 (d, J = 8.1 Hz, 1H), 7.92 (d, J = 8.3 Hz, 1H); ^{13}C NMR δ 102.8, 117.7, 119.2, 119.3, 121.4, 122.0, 122.7, 124.3, 128.8, 131.0, 131.7, 143.9, 152.3, 153.3, 161.1; HRMS calcd for $C_{21}H_{17}IN_2O_2S$ $(M\text{-}HI)^+$ *m/z* 361.101000, found *m/z* 361.101075.

4-[4-(3'-Ethoxycarbonyl-phenoxy)-phenyl]-thiazol-2-yl ammonium iodide (25). Isolated as a yellow solid (1.01 g, 64%); mp 158-160 °C; ^{1}H NMR (DMSO-d^6) δ 1.24 (t, *J* = 6.3 Hz, 3H), 4.24 (q, *J* = 7.0 Hz, 2H), 7.10 (s, 3H), 7.34 (d, *J* = 7.9 Hz, 1H), 7.45 (s, 1H), 7.51 (t, *J* = 7.7 Hz, 1H), 7.71 (d, *J* = 7.2 Hz, 2H), 7.94 (d, *J* = 7.9 Hz, 1H), 8.83 (br s); ^{13}C NMR δ 15.0, 62.0, 103.2, 109.8, 118.7, 119.6, 120.1, 124.8, 125.5, 129.0, 131.8, 132.8, 157.3, 157.9, 165.9, 171.0; HRMS calcd for $C_{18}H_{17}IN_2O_3S$ (M-HI)$^+$ *m/z* 341.095700, found *m/z* 341.095989; Anal. calcd. for $C_{18}H_{17}IN_2O_3S{\cdot}2\ H_2O$: C, 42.87; H, 3.37; N, 5.55. Found: C, 42.58; H, 3.26; N, 5.51.

4-(4'-Phenylsulfanyl-phenyl)-thiazol-2-yl ammonium iodide (26). Isolated as an orange solid (0.40 g, 98%); mp 129-132 °C; ^{1}H NMR (DMSO-d^6) δ 7.15 (s, 1H), 7.26-7.47 (m, 6H), 7.65 (d, *J* = 7.5 Hz, 2H), 7.81 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR δ 104.0, 127.7, 128.4, 129.0, 130.0, 130.7, 131.1, 132.5, 164.0, 170.8, 177.5; HRMS calcd for $C_{15}H_{13}IN_2S_2$ (M-HI)$^+$ *m/z* 285.052200, found *m/z* 285.052017.

4-[4-(4'-Chloro-phenylsulfanyl)-phenyl]-thiazol-2-yl ammonium iodide (27). Isolated as an orange solid (0.44 g, 98%); mp 158-160 °C; ^{1}H NMR (DMSO-d^6) δ 7.14 (s, 1H), 7.24-7.47 (m, 6H), 7.68 (d, *J* = 7.9 Hz, 2H); ^{13}C NMR δ 101.3, 110.1, 127.6, 127.9, 130.6, 132.0, 133.5, 143.6, 154.7, 167.8, 169.8; HRMS calcd for $C_{15}H_{12}ClIN_2S_2$ (M-HI)$^+$ *m/z* 319.012900, found *m/z* 319.013045.

4-[4-(3',4'-Dichloro-phenylsulfanyl)-phenyl]-thiazol-2-yl ammonium iodide (28). Isolated as a red solid (0.23 g, 48%); mp 45-47 °C (dec.); ^{1}H NMR (DMSO-d^6) δ 7.18 (s, 1H), 7.24 (s, 2H), 7.46 (d, *J* = 8.1 Hz, 2H), 7.59 (s, 1H), 7.69 (d, *J* = 7.7 Hz, 2H); ^{13}C NMR δ 104.8, 128.1, 131.2, 131.3, 132.2, 132.6, 132.8, 133.0, 133.2, 140.1, 150.3, 161.2, 171.1; HRMS calcd for $C_{15}H_{11}Cl_2IN_2S_2$ (M-HI)$^+$ *m/z* 352.974100, found *m/z* 352.974073.

4-[4-(4'-Methoxy-phenylsulfanyl)-phenyl]-thiazol-2-yl ammonium iodide (29). Isolated as an orange solid (0.40 g, 91%); mp 202-205 °C; ^{1}H NMR (DMSO-d^6) δ 3.74 (s, 3H), 6.98 (d, *J* = 8.3 Hz, 2H), 7.07 (s, 1H), 7.12 (d, *J* = 7.9 Hz, 2H), 7.40 (d, *J* = 8.1 Hz, 2H), 7.57 (d, *J* = 7.7 Hz, 2H); ^{13}C NMR δ 56.3, 103.4, 116.5, 116.7, 127.5, 128.4, 136.7, 140.3, 148.9, 154.3, 158.7, 169.7; MS APCI *m/z* 315 $(M\text{-}HI)^+$; Anal. calcd. for $C_{16}H_{15}IN_2OS_2$: C, 43.44; H, 3.42; N, 6.33. Found: C, 43.18; H, 3.40; N, 6.32.

4-(4'-*p*-Tolylsulfanyl-phenyl)-thiazol-2-yl ammonium iodide (30). Isolated as an orange solid (0.23 g, 54%); mp 182-185 °C; ^{1}H NMR (DMSO-d^6) δ 2.28 (s, 3H), 7.08 (s, 1H), 7.20 (m, 2H), 7.28 (d, *J* = 7.5 Hz, 2H), 7.62 (d, *J* = 7.9 Hz, 4H); ^{13}C NMR δ 21.2, 109.9, 127.6, 128.7, 129.2, 130.0, 131.4, 133.4, 140.5, 153.8, 156.5, 170.5; MS APCI *m/z* 299 $(M\text{-}HI)^+$; Anal. calcd. for $C_{16}H_{15}IN_2S_2$: C, 45.07; H, 3.55; N, 6.57. Found: C, 44.86; H, 3.52; N, 6.23.

NCI High Throughput PreScreen. Each cell line was inoculated and preincubated on a microtiter plate. Test agents were then added at a single concentration and the culture incubated for 48 h. End-point determinations were made with alamar blue.[15] Results for each test agent were reported as the percent of growth of the treated cells when compared to the untreated control cells. Compounds which reduce the growth of any one of the cell lines to approximately 32% or less (negative numbers indicate cell kill) were passed on for evaluation in the full panel of 60 cell lines over a 5-log dose range.

NCI Anti-tumor Screen. Compounds were tested against 60 human tumor cell lines at a minimum of five concentrations at 10-fold dilutions. A 48 h continuous drug exposure protocol[22] was used, and a sulforhodamine B (SRB) protein assay was used to estimate cell viability or growth.

Inhibition of Breast Cell Proliferation. MCF7 cells were treated with compounds or vehicle (DMSO). After a 48 h incubation, the SRB assay was used to determine inhibition of proliferation and cytoxicity.[23] Percent inhibition of growth at 100 μM was determined and GI_{50} values were calculated from log-dose response curves as previously described.[24]

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Tables

Table 1. Thiazoles

Cmpd #	X	R_1	R_2	R_3	% Yield
17	O	H	H	Cl	71
18	O	H	Cl	H	65
19	O	Cl	H	H	40
20	O	H	Cl	Cl	75
21	O	H	H	OMe	87
22	O	H	H	Me	65
23	O	H	H	Ph	70
24	O	H	H	OPh	86
25	O	H	CO_2Et	H	64
26	S	H	H	H	98
27	S	H	H	Cl	98
28	S	H	Cl	Cl	48
29	S	H	H	OMe	91
30	S	H	H	Me	54

Table 2. Human Breast Cancer Cytotoxicity Data.

Cmpd #	% Inhibition of MCF7 at 100 μM	GI_{50} (μM) MCF7	NCI/ ADR-RES	MDA-MB-231/ATCC	HS 578T	MDA-MB-435	BT-549	T-47D
16	81	ND	ND	ND	ND	ND	ND	ND
17	85	>100	>100	>100	>100	>100	>100	0.917
18	100	14.6	13.2	4.80	19.7	2.10	14.3	14.0
19	87	27.4	25.8	10.5	ND	14.8	12.8	16.4
20	47	3.02	1.29	2.29	2.00	0.759	1.91	20.9
21	24	ND	ND	ND	ND	ND	ND	ND
22	98	17.2	18.2	14.1	22.7	11.8	ND	0.54
23	53	14.3	17.4	12.6	18.8	18.6	10.4	3.91
24	81	35.1	35.9	12.6	27.8	22.7	16.1	4.9
25	84	ND	ND	ND	ND	ND	ND	ND
26	79	ND	ND	ND	ND	ND	ND	ND
27	89	21.6	17.5	12.4	18.8	1.49	15.3	24.4
28	54	5.68	3.37	3.73	ND	1.11	5.95	2.79
29	11	ND	ND	ND	ND	ND	ND	ND
30	96	25.9	64.6	>100	59.6	1.4	25.7	68

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